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Non-invasive positive pressure ventilation (NIPPV) in stable patients with chronic obstructive pulmonary disease (COPD)

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Chronic obstructive pulmonary disease (COPD);
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Summary While non-invasive positive pressure ventilation (NIPPV) has become an accepted management approach for patients with acute hypercapnia, it remains unclear whether it can also be beneficial in stable chronic obstructive pulmonary disease (COPD) patients with chronic respiratory failure. Randomised controlled trials (RCT) with a maximum duration of 3 months showed contradictory effects in blood gasses, dyspnoea, sleep efficiency and health-related quality of life. On the other hand, several uncontrolled trials did show positive results in patients with hypercapnia. Recently, an RCT compared the combination of NIPPV and long-term oxygen treatment (LTOT) with LTOT alone for a period of 2 years in hypercapnic patients. After this period dyspnoea decreased and health-related quality of life improved in the NIPPV compared to the LTOT group. Reasons for the contradictory results in the different trials are probably patient selection, adequacy of ventilation, and length of ventilation. Therefore, at this moment there is no conclusive evidence that NIPPV should be provided routinely to stable patients with COPD. However, a selected group of patients might have clinical benefits from it. Patients who are clearly hypercapnic, who can tolerate an effective level of ventilatory support, and who get enough time to adjust to the ventilator might show clinical benefits even after 3 months. A trial with ventilatory support in this group of patients can be considered.

Introduction

Chronic obstructive pulmonary disease (COPD) is currently one of the leading causes of death in the world and further increases in the prevalence are predicted. Even with optimal medication, patients with COPD often suffer from dyspnoea that limits their exercise tolerance and impairs health-related quality of life. Respiratory rehabilitation has shown by a number of randomised controlled trials (RCTs) that it improves dyspnoea, exercise tolerance and health-related quality of life.[1–4] Therefore, rehabilitation has become now part of the standard of care for the more severely affected patients. Newer approaches to the management of COPD such as lung transplantation and lung volume reduction surgery (LVRS)[5] are probably only beneficial in a selected group of patients.

While short-term non-invasive positive pressure ventilation (NIPPV) has become an accepted management approach for patients with acute hypercapnia, it remains unclear whether it can also be beneficial in stable COPD patients with chronic respiratory failure. Two hypotheses for effectiveness of NIPPV in stable patients with COPD have

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been discussed recently.[6] The first one is that NIPPV can be effective in resting the respiratory muscles. Due to hyperinflation the diaphragm operates at a disadvantageous position on its length–tension curve. As shown by Bellamare and Grassino, a number of factors all represented in the time tension index (TTI) contribute to the development of diaphragmatic fatigue.[7] This index contains the inspiratory load, represented by the pressure generated by the diaphragm during each breath (P_{di}) as a proportion of maximal force generated by the same muscle (P_{dimax}) multiplied by the duty cycle represented by the inspiration time (T_i) divided by the total time of the respiration (T_{tot}). In formula $TTI = (P_{di}/P_{dimax} T_i/T_{tot})$. If the TTI exceeds 0.15, fatigue of the diaphragm may occur. The theory behind NIPPV is that it alleviates fatigue by improving inspiratory muscle capacity; however, this has not been proven yet. The second hypothesis contains the sleep theory. Many investigators have shown that sleep quality is poor in patients with severe COPD. In addition, they have frequently desaturations together with periods of hypoventilation. NIPPV may reduce the number of arousals and so improving sleep quality. In addition NIPPV may prevent worsening of nocturnal hypoventilation, thereby possibly resetting the respiratory centre for CO_2. Finally, this will lead to an improved daytime ventilation.

This paper will review the papers that have been published investigating the effects of NIPPV in stable patients with COPD classified by the design of the study, i.e. controlled and uncontrolled. The different outcomes of these studies will be discussed leading to a conclusion where we stand now with regard to NIPPV in stable patients with COPD.

Randomised controlled trials

RCTs were identified from several sources, like Medline, Embase, and Cumulated Index to Nursing and Allied Health (CINAHL). In addition, records were identified through hand searching of abstracts from meetings of the American Thoracic Society, the American College of Chest Physicians, and the European Respiratory Society. We included in this review both nocturnal NIPPV as well as daytime NIPPV if they have been published as a full paper. Patients in the treated group by NIPPV continued to receive their usual management for COPD. The control group received the same management as the study group with the exception of their not receiving NIPPV.

Short-term NIPPV

Until now five RCTs with a maximum duration of 3 months have been published as a full paper.[8–12] Details of the studies are presented in Table 1. Strumpf et al. published the first study in 1991 and except for neuro-psychological function no significant changes were detected.[11] The reason for this result might be due to the fact that only 7 out of the 19 patients completed it, which under-powers the study. In addition, the patients were not particularly hypercapnic, while some patients were even normocapnic. Gay et al. assessed the effects of NIPPV in hypercapnic patients and showed that NIPPV did not lead to an improvement in clinical parameters.[10] Again, in this study, only a small number of patients completed the study. In contrast to the previous studies Lin et al. determined the effects of NIPPV after 2 weeks and found only a positive effect of the combination of NIPPV and oxygen on the nighttime oxygenation.[8] The reason for their negative result might be that some patients need more than 2 weeks of acclimatisation before they become comfortable and feel confident with the ventilator during the night. Meecham Jones was the only study that showed clear evidence of clinical benefits for nocturnal NIPPV in patients with COPD.[9] After 3 months the combination of NIPPV and oxygen was better than oxygen alone for gas-exchange, sleep efficiency and health status. Renston et al. investigated the effects of daytime NIPPV (2 h a day for 5 consecutive days).[12] Despite the fact that no significant changes were found in gas-exchange, patients in the Bi-level Positive Airway Pressure (BiPAP) group showed both a significant decrease in level of dyspnoea and an improvement in 6-min walking distance (6-MWD). However, it does not become clear from the paper if BiPAP is significantly better than sham treatment. We did not include the study of Diaz et al. in our overview of the RCTs as no full paper had been published yet.[13]

Recently, a meta-analysis of individual data from RCTs was carried out comparing NIPPV with conventional management of patients with COPD and stable respiratory failure. RCTs were identified from several sources.[14] Only studies investigating nocturnal NIPPV via a nasal or facemask for at least 5 h each day for at least 3 weeks were included. Patients in the actively treated group continued to receive their usual management for COPD next to NIPPV. The control group had to have received the same management as the study group with the exception that they did not receive NIPPV. We were able to find 4 RCTs that fulfilled the above-mentioned criteria (Table 2)[9–11,15] Three months

Table 1 Randomised controlled trials of short-term NIPPV.

Trial	Number of patients (treatment/controls)	FEV_1 mean (range)	$PaCO_2$ mean (range)	Length (months)	IPAP/EPAP	Outcome measures	Effects
Strumpf et al.[11]	Cross-over trial (enrolled: 19, completed: 7)	0.54 (0.46–0.88)	49 (35–67)	3	15/2	ABG, RM, walking test, dyspnea, PFT, sleep study, NP function	Significant effects for NP function
Gay et al.[10]	Parallel-group trial (randomised: 7/6, completed: 4/6)	0.68 (0.5–1.1)	55 (45–89)	3	10/2	ABG, 6-MWD, dyspnoea, PFT, sleep study	No significant effects
Meecham-Jones et al.[9]	Cross-over trial (enrolled: 18, completed: 14)	0.86 (0.33–1.7)	56 (52–65)	3	18/2	ABG, 6-MWT, HRQL, PFT, sleep study	Significant effects for ABG, sleep efficiency, HRQL
Lin[8]	Cross-over trial (enrolled: 12, completed: 12)	33% pred.	51(±4)	2 (week)	12/2	ABG, PFT, RVEL, LVEF, sleep study	Significant effects of NIPPV and O_2 on nocturnal oxygenation
Renston[12]	Parallel-group trial (randomised: 9/8, completed: 9/8)	0.75 (0.45–1.05)	—	5 days for 2 h	15–20/2	ABG, EMG, RM, 6-MWD, dyspnoea	Significant effects for dyspnoea and 6-MWD

data of the study of Casanova were included as well.[15] The study of Lin was excluded because their intervention period was 2 weeks,[8] while the study of Renston was excluded because of daytime ventilation.[12] The long-term study of Clini was not included because it had not been published as a full paper at the time we did our analysis.[16] Table 2 shows that 3 months of NIPPV in patients with stable COPD did not improve lung function, gas-exchange, or sleep efficiency. The high upper limit of the confidence interval for the 6-MWD suggests that some people did improve their walking distance, while, on the other hand, the wide confidence interval suggests also that some might have a deterioration in 6-MWD. Currently, it is not possible to identify a patient who will improve his 6-MWD before putting them on NIPPV. Due to a limited number of included patients in this meta-analysis, a clear clinical direction regarding the effects of NIPPV in COPD cannot be provided.

Long-term NIPPV

Casanova et al. were the first to set up a long-term trial with a duration of 1 year.[15] They randomised 52 patients to either NIPPV plus standard care or to standard care alone. The level of BiPAP was modest (IPAP 12–14 cmH_2O) and its effect was not controlled during the night. After 3 months the number of hospital admissions was less (5% versus 15%), but this benefit was not seen at 6 months. After 12 months there were no significant changes in arterial blood gasses and respiratory muscle strength, whilst there were modest improvements in dyspnoea and neuro-psychological function. Recently, Clini et al. reported a prospective, randomised, controlled trial comparing the combination of NIPPV and long-term oxygen treatment (LTOT) with LTOT alone for a period of 2 years.[16] Only patients with a $PaCO_2 > 6.6$ kPa were included. One hundred and twenty patients were considered, 90 were randomised and 47 completed the study. The level of NIPPV was modest (IPAP of 14 ± 3 cmH_2O), but they used the ventilator for a considerable number of hours (9 ± 2 h). Compared with the period before the study, total hospital admissions increased by 27% in the LTOT group whilst it decreased by 45% in the NIPPV group. ICU admissions decreased with NIPPV by 75% and 20% in the LTOT group. However, both outcomes were not significantly different between groups. After 2 years dyspnoea decreased and health-related quality of life improved in the NIPPV compared to the LTOT group. The study of Clini suggests that NIPPV could have beneficial effects in patients with COPD; however, these

Table 2 Primary results of a meta-analysis on nocturnal NIPPV.

Outcomes	Contributing trials (references[a])	Sample size (NIPPV/control)	Treatment effect	
			Mean	95% CI
FEV_1	9,10,11,15	33/33	0.02 l	−0.04, 0.09
FVC	9,10,11,15	33/33	−0.01 l	−0.14, 0.13
P_{imax}	10,11,15	24/24	6.2 cmH_2O	0.2, 12.2
P_{emax}	10,11,15	24/24	18.4 cmH_2O	−11.8, 48.6
PaO_2	9,10,11,15	33/33	0.0 mmHg	−3.8, 3.9
$PaCO_2$	9,10,11,15	34/33	−1.5 mmHg	−4.5, 1.5
6-min walk test	9,10	12/11	27.5 m	−26.8, 81.8
Sleep efficiency	9,10,11	13/11	−4.0%	−14.7, 6.7

[a]Contributing trials: Meecham Jones et al.[9], Gay et al.[10]; Strumpf et al.[11]; Casanova et al.[15].

improvements were not sufficiently large to advocate the widespread use of NIPPV in these patients. The long-term trial of Muir et al. was not included in this systematic overview of RCTs as no full paper had been published yet.[17]

Uncontrolled trials

In contrast to above-mentioned RCTs, most uncontrolled trials of NIPPV showed positive results. Elliot et al. showed significant effects of nocturnal NIPPV on gas-exchange in 8 patients with severe COPD (mean FEV_1 0.53 l) and hypercapnia (mean $PaCO_2$ 8.0 kPa).[18] The change in decrease in $PaCO_2$ was significantly correlated with a decrease in both RV and gas trapping and with an increase in ventilation. They did not find that the improvements in gas-exchange were due to a relief of muscle fatigue. Another study from this group, including 12 patients, showed after 12 months of NIPPV a significant decrease in $PaCO_2$ and improved sleep efficiency, while the quality of life was unchanged.[19] In contrast, Perrin et al. showed that quality of life improved significantly by 6 months of NIPPV. In this study, 14 patients with a mean $PaCO_2$ of 7.8 kPa received volume ventilation during the night.[20] Beside an improved quality of life they also reported significantly improved gas-exchange. The same positive results were seen in the study of Sivasothy.[21] Twenty-six patients with severe COPD (mean FEV_1 0.7 l) and hypercapnia ($PaCO_2$ 8.6 kPa) were ventilated by a volume ventilator during the night. After 18 months (range 4–74) both gas-exchange and quality of life improved significantly. Another long-term study of Jones et al. showed after 24 months of pressure ventilation significant improvements in gas-exchange and reduction in hospital admissions general practitioner visits.[22] In summary, these uncontrolled studies showed that in a selected group of patients (with severe hypercapnia) NIPPV can improve gas-exchange. However, this does not lead to a concomitant decrease in pulmonary artery pressure, as shown recently.[23] Despite these positive findings, we have to be careful with its clinical implications, as these studies did not include an adequate control group who received otherwise the same medical management.

Discussion

It is obvious that the studies we reviewed in this paper do not present a clear picture as to whether NIPPV in stable COPD is beneficial or not. In the next section the rationale for NIPPV and issues that might explain the differences in outcome will be discussed.

Theoretical basis for NIPPV

There are some theoretical reasons why NIPPV might be effective: (1) resetting the respiratory centre to improve daytime gases, (2) resting dysfunctional respiratory muscles thereby increasing their daytime strength and endurance, (3) improving peripheral muscle function from a better milieu (pH, PaO_2, $PaCO_2$), and (4) preventing the repeated nocturnal arousals thereby improving the quality of sleep. In fact, only muscle rest and sleep quality have been investigated in different studies. Resting inspiratory muscles was the hypothesis behind a major trial of negative pressure ventilation (NPV). Shapiro et al. randomised 184 patients with severe COPD to active or sham ventilation with a poncho wrap negative pressure ventilator.[24] There were no significant changes in respiratory

muscle strength; however, whilst patients were encouraged to use the ventilator for at least 5 h each day, the average duration of use was closer to 3 h and the intensity of the treatment intervention was quite variable. Celli[25] and Zibrak[26] also failed to identify improvements in arterial blood gases or respiratory muscle strength with NPV.

In contrast, studies that included patients with higher $PaCO_2$ levels showed improvements in respiratory muscle function after NPV.[27] One uncontrolled study showed that NIPPV had induced a significant decrease in $PaCO_2$ in association with a decrease of the pressure–time product of the diaphragm. There also appeared to be a subgroup of responders who had a significantly increased trans-diaphragmatic pressure and were better capable to clear CO_2.[28] In addition, Belman et al. showed that positive pressure ventilation was more effective in unloading the diaphragm compared to NPV.[29] So, there is some evidence that NIPPV can be effective in unloading the respiratory muscles; however, this comes only from uncontrolled trials. In contrast, none of the RCTs found a significant improvement in respiratory muscle function.

Another theoretical explanation for the effects of NIPPV is improved sleep efficiency. Five out of 7 RCTs did carry out a formal sleep study. Only Meecham Jones, who measured the effectiveness of ventilation in clearly hypercapnic patients, showed an improved sleep efficiency.[9] In an uncontrolled very short-term trial of 3 days, Criner et al. investigated gas-exchange and sleep efficiency in patients with COPD.[30] They compared low-level continuous positive airway pressure with BiPAP on 2 consecutive nights in patients with a mean PaCO2 of 58($\pm$4) mmHg. No significant changes were found in $PaCO_2$, but there was a significant improvement in sleep efficiency and total sleep time.

In conclusion, there are currently no studies on NPV or NIPPV that have provided evidence as to whether the benefits they found in gas-exchange were related to improvements in respiratory muscle function or in sleep efficiency.

Selection of patients

Patients who are more hypercapnic seemed to have more benefits from NIPPV. The RCTs from both Meecham Jones[9] and Clini[16] both showed significant benefits in different outcome parameters. In contrast to other RCTs, they did not include patients with a $PaCO_2$ under 6.6 kPa (see Tables 1 and 3). In addition, Meecham Jones showed that the patients who had an increase of $PaCO_2$ during the night before they were on NIPPV had the most benefit in decreasing daytime $PaCO_2$ after starting NIPPV (Fig. 1). The other RCTs did include normocapnic patients[11,15] or patients who were mildly hypercapnic.[7,9] The uncontrolled studies that included only hypercapnic patients (lowest value of 6.3 kPa) also had positive outcomes. In our meta-analysis we

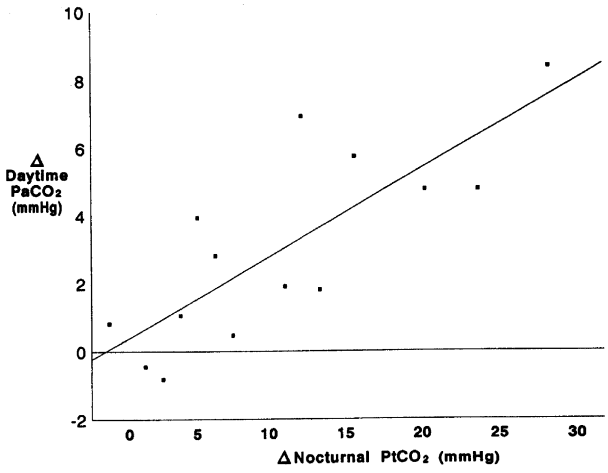

Figure 1 Correlation between change in daytime arterial $PaCO_2$ and the change in mean overnight transcutaneous P_{CO_2} for individual patients ($r = 0.69$; $p = 0.01$).

Table 3 RCTs of long-term nocturnal NIPPV.

Trial	Type of trial numbers patients (treatment/ controls)	FEV_1 mean (range)	$PaCO_2$ mean (range)	Length (months)	IPAP/EPAP	Outcome measures	Effects
Casanova et al.[15]	Parallel-group trial (randomized: 26/26, completed: 17/19)	0.85 (0.44–1.28)	51 (37–66)	12	12–14/4	ABG, RM, dyspnea, PFT	Significant effect for dyspnoea and NP function
Clini[16]	Parallel-group trial (randomised: 43/47, completed: 23/24)	0.70 (0.30–1.35)	55 (50–75)	24	14/2	ABG, RM, dyspnoea, sleep study, HRQL, hospitalisations	Significant long-term effects for dyspnoea and HRQL. Positive trends for hospital admissions and ICU stay

expected heterogeneity between the four studies based on different levels of $PaCO_2$ at inclusion; however, we could not detect such a difference, probably because of the low number of patients included in this analysis. Nevertheless, all available studies do suggest that patients who are more hypercapnic might benefit from NIPPV. In addition, as published recently, it might be important to identify unstable patients ($\geqslant$2 hospitalisations due to respiratory failure in a 12-month period) who might have benefited by chronic ventilatory support.

Adequacy of ventilation

At this moment there is no evidence that pressure-cycled ventilation is better or worse than volume cycled. At the same time it is remarkable that all RCTs using BiPAP showed both positive and negative results, while the uncontrolled studies used mainly volume-cycled ventilation and showed positive effects. While there is no study comparing both types in COPD patients only, Schonhofer et al. did compare pressure-controlled ventilation with volume-controlled ventilation in patients with respiratory failure.[31] They concluded that the majority of the patients who were initially satisfactorily ventilated with a volume ventilator could also adequately be ventilated with pressure ventilation. However, currently there is no evidence that either type is preferable in patients with COPD.

Assist-control ventilation is frequently selected as the mode of choice to enhance synchrony between patient and ventilator. One study did use time-cycled ventilation to reduce the level of inspiratory muscle effort; however, asynchrony between patient and machine was present in 20%.[11] More important than the type of ventilation might be the assessment as to whether the ventilation was effective. Meecham Jones[9] was the only study that assessed the adequacy of ventilation by transcutaneous $PaCO_2$, while Strumpf assessed it occasionally using end tidal CO_2.[11] The latter might easily miss hypoventilation, leading to ineffective ventilation. In all other studies[8,10,12,15,16] the effectiveness of ventilation was not assessed, so a full evaluation of the efficacy cannot be made. This means that we do not know whether the inspiratory pressure that were used were high enough. In the study of Meecham Jones, mean inspiratory pressures of 18 cmH_2O were used. These investigators probably found that they needed these higher levels to achieve effective ventilation. This might explain why other studies, that did not assess their ventilatory effectiveness, used lower pressures and did not find beneficial effects of NIPPV. Finally, since it takes time for the patient to get used to the mask and for the clinician to find the appropriate settings of the ventilator, it seems better to admit the patients to the hospital. In this way, effective ventilation can be achieved, as shown in the study of Meecham Jones.[9]

Number of hours on NIPPV

Since it is not known what is the optimal duration of ventilatory support, different approaches have been used. There are two randomised controlled studies[12,13] treating patients with COPD for a short period with ventilatory support during the day. In one, the patients received BiPAP for 2 h daily for 5 days a week, while in the other BiPAP was given for 3 h daily, 5 days a week for 3 consecutive weeks. These short periods produced significant benefits in clinical parameters. However, without a parallel improvement in gas-exchange it is difficult to understand the underlying mechanism.[12] At the same time, 5 days seem to be a short time for the patients to adjust to the machine. Still these two studies showed that physiological improvements could be assessed by very short-term periods of ventilatory support. Other studies with positive outcomes showed that a considerable number of hours are effective. In the long-term trial of Clini the mean number of hours on BiPAP was 9 ± 2 h.[16] In the study of Meecham Jones the median number of hours was 6.9 h (range 4.2–10.8).[9] Until now there is no study showing that more hours on ventilatory support is better in reducing the work of breathing, resting the respiratory muscles or improving sleep quality. Probably because it is practical NIPPV has been advocated to use it during the night as long as possible.

Length of ventilation

The length of ventilatory support can also influence the outcomes. Most studies were of relatively short duration (3 months) and some of them could detect significant clinical benefits after such a short period. Two European studies followed the patients for the longest period.[16,17] Clini et al. showed an improved quality of life after 2 years (Fig. 2) and an improved dyspnoea already after 1 year.[16] In addition, they showed a reduction in both hospital admissions and ICU admissions. Cumulative days spent in hospital due to respiratory exacerbations showed a trend in favour of those receiving NIPPV (12.6 ± 7.9 versus 16.9 ± 10.3), respectively. Muir

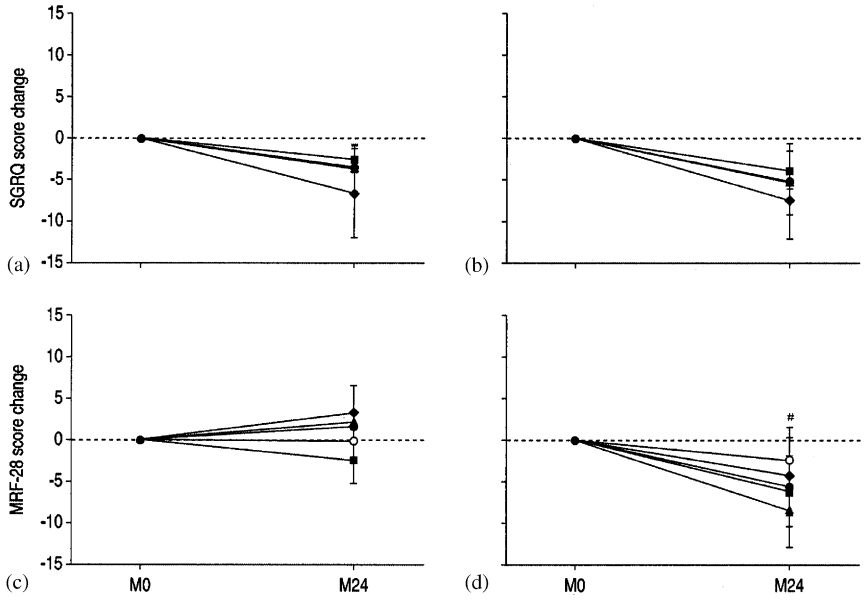

Figure 2 Change from baseline in total and dimension scores of the St. George's respiratory Questionnaire (SGRQ) (a and b) ((♦) symptoms; (■) activity; (▲) impact; (●) total) and the Maugeri Foundation Respiratory Failure Questionnaire (MRF-28) (c and d) ((○) cognitive behaviour; (♦) activity; (■) disability; (▲) others; (●) total). M0: discharge; M24: 24 months after discharge. Group comparison for changes from baseline in total SGRQ score was not significant, while it was significant in MRF-28 score ($p = 0.041$).

compared 60 patients with severe COPD who received LTOT and NIPPV with 62 patients who received LTOT alone.[17] After a median follow-up of 4.7 years there were no significant differences in survival between the groups, with the exception of patients older than 65 years in whom survival was better in the NIPPV + LTOT group. In contrast to these long-term studies patients in the study of Meecham Jones needed only 3 months to get significant clinical benefits.[9]

Summary

In conclusion, there is currently no conclusive evidence that NIPPV should be provided routinely to stable patients with COPD. Still, a selected group of patients might have clinical benefits from it. Patients who are clearly hypercapnic, who can tolerate an effective level ventilatory support, and who get enough time to adjust to the ventilator might show clinical benefits even after 3 months. A trial with ventilatory support in this group of patients can be considered.

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